Measuring selection for genes that promote long life in a historical human population

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SUMMARY: The unusually long lifespans of humans and the persistence of post-reproductive lifespan in women represent evolutionary puzzles because natural selection cannot directly favour continued living in post-menopausal women or elderly men. Suggested sources of indirect selection require genetic correlations between fitness and survival or reproduction at younger ages, reproduction in the opposite sex, and late-life contributions to offspring or grand-offspring fitness. We apply quantitative genetic analyses to data from a historical human population to explicitly test these evolutionary genetic hypotheses. Total genetic selection increased male post-50 lifespan by 0.138 years/generation; 94% of this arose from indirect selection acting to favour early-life fitness in both sexes. These results argue strongly against life-history models of ageing that depend upon trade-offs between reproduction and late-life survival, No source of indirect selection for female post-50 lifespan was detected, deepening the mystery of why female post-reproductive survival persists. This result is likely due to recent changes in the genetic architecture of female lifespan, and it highlights the need for similar quantitative genetic analyses of human populations at other points along demographic transitions.

MAIN: Natural selection favours increased lifespan whenever continued living is expected to yield future reproductive dividends, and this expectation declines with advancing age in humans of both sexes [1]. In males, the prevailing assumption is that late-life reproduction selects for late-life survival [2], but this hypothesis remains untested, and males often succeed in living long beyond the last ages of male reproduction [3]. In females, the late-life attenuation of phenotypic selection is more extreme, as menopause reduces this selective force to zero in middle age. Nevertheless, even women in primitive hunter-gatherer and horticultural populations can live many decades post-menopause [4-6] in apparent violation of simple evolutionary predictions that late-acting deleterious mutations should accumulate unchecked [7] (or even aided [8]) by natural selection. Whilst there is controversy regarding the precise mechanisms for the genesis of post-reproductive lifespan [9-11], evolutionary theory requires that its continued persistence must be explained by selection for traits with which it is genetically correlated (indirect selection).

Three evolutionary mechanisms have been suggested to explain the maintenance of post-reproductive lifespan. The 'inter-age correlation model' proposes that genes for early age survival or reproductive function also benefit late-age survival [12]. The 'inter-sex correlation model' proposes that late-life survival genes are shared between the sexes [2,13]. Because males do not menopause, selection for these genes in men can favour post-menopausal survival in females. The '(grand) maternal models' suggest that prolonged lifespans of maternal or grandmaternal caregivers conveys a fitness advantage to the related recipients of that care. When the genes for caregiving and late-life survival effects are shared, care may generate indirect selection for late-age survival in females [7,14,15]. To describe this mechanism in quantitative genetic terms, we must invoke the concept of 'indirect genetic effects' or IGEs [16]; these are the effects that genes have upon the phenotypes of social partner(s). IGEs differ from 'direct genetic effects', or DGEs; the influence that one's own genes have on one's own

phenotype. The '(grand)maternal models' require a positive genetic correlation between the caregiver-derived IGEs for fitness and the DGEs for lifespan. By predicting an evolutionary response of late-life survival to selection to counter the deleterious effects of new mutations, all three models assume that positive genetic correlations between late-age lifespan and fitness have arisen and are maintained by recurrent mutation. Whilst some studies have demonstrated phenotypic correlations and associations that are consistent with grand-mother effects [4,17], for example, evidence for a positive genetic correlation represents the "smoking gun" necessary to demonstrate the true efficacy of an evolutionary pathway to maintain post-reproductive survival. Before now, no study has estimated these key genetic parameters, and as a result no quantitative assessments of these evolutionary pathways have been attempted.

We resolve this gap in our understanding by applying 'Animal Model' quantitative genetic analyses [18] to estimate genetic correlations between post-reproductive lifespan and sex-specific fitness components. 'Animal Models' have been used in the past to infer evolution by natural selection of life history traits in other historical human populations [19,20]. We use these genetic correlations in conjunction with estimates of phenotypic selection gradients [21] to quantitatively compare the importance of candidate evolutionary pathways to explain the persistence of post-50 lifespan in both sexes. 50 years of age was chosen as it approximates the age at menopause in humans [22], and it has been used previously as a reference age for describing post-reproductive lifespan in humans [17]. Human phenotypic and pedigree data comes from a subset of the Utah Population Database [23,24], which derives from a population of pioneers of the American west that colonized the Utah Territory beginning in 1847. The primary subject cohort comprises all individuals born between 1860 and 1889 and their siblings (n = 128,129). This population was chosen as it was recent enough to present sufficient data to permit powerful statistical analyses while old enough to exhibit natural fertility and other features of a less-

modern environment [23]. Pre-historical, hunter-gatherer and modern populations are each lacking in one or more respect.

Each individual was associated with values for relative fitness (*w,* the relative contribution of an individual to the next generation that is properly defined in the context of an age-structured population as the individual reproductive value at birth – see Methods) and a number of sex-specific traits: the number of years survived beyond 50 (LS_{50}); fitness accumulated prior to 50 (w_1); survival to 50 (P_{50}); and fitness accumulated at 50 and greater (w_2). We take a three-part approach to investigating genetic selection for late life survival. First, we estimate the genetic covariation between fitness and sex-specific LS_{50}. This both predicts a response to selection and provides an estimate of total selection acting to increase genetic values for late-life lifespan. We then investigate at a finer scale the degree to which specific hypothesized sources of selection act to favour (or disfavour) post-50 survival genes in both sexes. This requires a careful articulation of the various evolutionary models put into a quantitative genetic perspective. This is the motivation for the second part of our study, which is to provide a unified conceptual model for the genetic selection of post-reproductive female lifespan that both: 1) generalizes across all previous evolutionary genetic hypothesis and 2) parameterizes these hypotheses in terms of estimable quantitative genetic values. To distinguish amongst these evolutionary models, we then estimate the parameters from this conceptual quantitative genetic model and thus estimate the degree to which selection for post-50 lifespan genes is driven by direct selection or indirect selection via inter-age, inter-sex, or (grand)maternal effects.

RESULTS

1. Estimating net genetic selection for late-life lifespan. Significant heritability was found for w ($h_w^2 = 0.118, se = 0.006$); this is within the range of other estimates of the heritability

of fitness in natural animal populations (collared flycatcher = 21±6% (female), 7±6% (male)[25]; red deer = 8.6±2.3% (females), 3.5±3.1% (males) [26]; female soay sheep = 2.6±1.5% [27]; great tits = 0.2±3% (females), 2±4% (males) [28]. Sex-specific lifespan was also heritable ($h^2_{♀LS_{50}} = 0.176,\ se = 0.009$ and $h^2_{♂LS_{50}} = 0.232,\ se = 0.010$) (Table 1). These estimates appear to be slightly lower than results from Danish twin studies (0.26-0.33) [29,30]; one of these studies reported slightly lower heritability in females [29], but it attributed this to higher environmental variance. Our results find greater environmental (105.09 yr^2 vs 93.04 yr^2) but lower genetic variance (23.83 yr^2 vs 29.0 yr^2) in females vs males. An 'Animal Model' study of a preindustrial Finnish population estimated the heritability of female and male post-15 lifespan to be 0.175 and 0.167, respectively [20]. These estimates were similar to our estimates of post-50 lifespan, but with associated standard errors of 5-10 times greater.

These significant heritability estimates indicate that post-50 lifespan had the potential to evolve by natural selection in both sexes. However, whilst there was significant net selection acting to increase the genetic values for male lifespan in males (by 0.138 years/generation), the estimate of genetic selection for females post-50 lifespan was insignificant (Table 2): fitness was genetically correlated to ♂LS_{50} ($r_g = 0.110, se = 0.031$) but not to ♀LS_{50} ($r_g = -0.050,\ se = 0.034$). Genes tended to have the same effects upon post-50 lifespan in both sexes, but this tendency was not absolute as inter-sex genetic correlations for LS_{50} were high $\left(r_g = 0.817,\ se = 0.032\right)$ but significantly less than one ($p < 0.0001$; Table 2 and Supplementary Table 4). This suggests that at least some sex-independent lifespan genes that have beneficial effects on male fitness are neutral or deleterious in females. This allows the difference in genetic selection for lifespan between males and females.

2. Conceptual quantitative genetic model for the evolution of late-lifespan. The pathways by which selection might act to increase lifespan beyond some age *Y* (after which there is no

female reproduction) are illustrated in Fig. 1. Each pathway is identified individually in the figure as a product of a phenotypic selection gradient (straight arrows **A**-**C**), genetic variance (straight arrows **D** – **J**), and genetic correlations (curved arrows **K**-**S**). The last includes relatedness between social partners (**R**), as this is the within-trait genetic correlation among individuals. Direct genetic selection for male lifespan at some age *Y* is **BISH**, and indirect selection for male lifespan may derive from a genetic correlation with early female (**ADKH**) or early male (**CJQH**) fitness. Direct selection for post-*Y* lifespan genes in females is impossible (as *Y* is defined as the age beyond which females don't reproduce), but indirect selection can come from: the 'inter-age correlation model' (a genetic correlation with early female fitness **ADLE** or early male fitness **CJME**), the 'inter-sex correlation model' (a genetic correlation with late male fitness **BINE)**, and the '(grand)maternal model' *via* early female fitness (**AFRPE**) or male fitness (**CGROE**) (see below for a more detailed explanation of this model). Pathways that connect genetic values of lifespan to fitness through other identified intermediates are possible (and these may, in principle, contribute to a response to selection). However, some are not highlighted explicitly here because they have either not been suggested elsewhere to be important or they have been found in this study to be insignificant contributors to the genetic selection of post-*Y* lifespan.

To understand the '(grand)maternal model' in more detail, imagine an allele that improves female survival post-*Y* in a focal individual (contributes to the genetic value $♀G_{LSY}$), where the focal individual is the (grand) offspring. Under the (grand)maternal effect model, for this allele to be selected to increase in frequency in focal individuals, it must be genetically correlated (paths **P** or **O**, depending upon the sex of the affected (grand)offspring) with an allele that causes (grand)mothers to improve the fitness of their (grand)offspring (the latter is an indirect genetic effect that contributes either to $♀_{w1}{}^{*}$ or $♂_{w1}{}^{*}$). This allele has no direct effect on the fitness of the focal individual when expressed in the (grand)offspring, but it has an indirect

effect because it is present in the (grand)mother of the focal individual as a result of relatedness (path R, contributes to $♀_{w1}^{**}$ or $♂_{w1}^{**}$). (Grand)mothers affects the fitness of focal individuals via the action of the indirect effect allele (path **F** or **G**) and thus allows indirect selection both on the indirect effect allele [16] and the allele that improves post-*Y* survival. From an inclusive fitness perspective [31], kin selection for the (grand)maternal effect genes $♀G_{w1}^{*}$ or $♂G_{w1}^{*}$ derives from the product of relatedness between the (grand)mother and (grand)offspring (**R**) and the fitness benefit of the effect to (grand)offspring fitness genes (**AF** or **CG**). As we are interested in selection for post-*Y* lifespan genes, $♀G_{LSY}$, through (grand)mother effects, we find the correlated response to selection by multiplying kin selection for $♀G_{w1}^{*}$ or $♂G_{w1}^{*}$ by the correlation (**P** or **O**) between these genes and those for the post-*Y* lifespan genes. Finally, changes in genetic values for lifespan are manifested on this phenotype in proportion to its amount of genetic variation, **E.**

3. Distinguishing evolutionary models of late-life lifespan. We parameterised all of the relevant pathways in Fig 1. All traits were significantly heritable, with the exception of $♀w_2$ (Table 1). The last confirms the expected lack of genetic variance in late-life fitness in females and thus no potential for direct selection for female late-life survival genes; this trait was not considered in the subsequent analyses. No traits had significant IGE variation derived from mothers. In fact, four traits (*w,* $♀w_1$, $♂w_1$, and $♂P_{50}$) had significant maternal effects (Supplementary Table 1), but the lack of IGE variation must be interpreted to mean that while mothers influenced the phenotypes of their children, this influence was not heritable. Total fitness had significant maternal and grandmaternal effects arising through both the maternal and paternal grandmothers, but these also had no significant genetic basis (Table 1 and Supplementary Table 1), and were therefore not heritable. Because genetic covariance cannot exist in the absence of genetic variation, there was no evidence to support either the maternal

166 or grandmaternal effects model of indirect selection for late-life lifespan in either sex (i.e.,
167 neither the path **P** in **AFRPE** nor the path **O** in **CGROE** can exist).

168 We estimated genetic correlations between male and female LS_{50} and all remaining fitness-
169 related traits (Table 3). All showed positive genetic covariance with ♂LS_{50}, but only ♀P_{50} and
170 ♂P_{50} covaried with ♀LS_{50}. Phenotypic selection gradients for the fitness-related traits were
171 estimated by multiple regression [32] (Table 4). Each of these gradients multiplied by the genetic
172 covariance between that trait and sex-specific LS_{50} (Table 3) defines that trait's independent
173 contribution to the per-generation evolutionary change in sex-specific LS_{50} (Figure 1 and Table
174 5). The sum of estimates of genetic selection for male LS_{50} (+0.156 years/generation) was
175 within half of the standard error of the estimate of total selection for male LS_{50} genes (+0.138
176 years/generation), indicating that both methods agreed (the total covariance estimated in Part
177 1 equalled the sum of partial covariances estimated in Part 3). Direct selection for male late-
178 life lifespan was relatively weak; late-life fitness explained only 4.6% of the genetic selection
179 for late-life survival. Selection for male late-life survival genes was almost entirely driven by
180 indirect selection for male and female early life fitness (w_1), explaining 38 and 55% of the
181 selection for male late-life lifespan genes, respectively.

182 Antagonistic selection for different components of fitness could not explain the lack of
183 overall genetic selection for late-life female lifespan, as no component source was
184 independently significant: indirect selection for female late-life lifespan was weak as a result
185 of either weak genetic correlations (as with early fitness in both sexes and late male fitness) or
186 weak phenotypic selection for the correlated traits (survival to 50 in both sexes). Thus
187 reweighting the relative strength of phenotypic selection on different fitness components, such
188 as might happen by shifts in mating system that emphasize phenotypic selection for late-age
189 male fertility [2] cannot result in net selection to favour ♀LS_{50} genes.

This study represents the first attempt to quantify the relative importance of alternative evolutionary models of late-life survival in humans. We find very high genetic correlations between female and male lifespan (+0.817), which is a degree of association that is usually associated with strictly constrained evolutionary pathways. Nevertheless, we find very different predicted responses to selection for female and male lifespan. Whilst our results show that natural selection did favour LS_{50} genes in males, we found no selection for late-life survival genes in females. This is very surprising because females appear to live at least as long as men in hunter-gather populations [33-35], and a simple evolutionary explanation for this relationship requires that selection for late-life survival in female genes must be at least as strong as selection in male genes. Because this is the first study to explicitly measure selection for post-reproductive lifespan genes in human females, we cannot say whether this null relationship is general to all recent human populations, but we can suggest possible explanations for the apparent disassociation between fitness and female post-50 lifespan genes in the Utah population:

Perhaps genetic (grand)maternal effects upon fitness did exist in the population, but our pedigree was too shallow to detect these. This seems unlikely given that the pedigree for the 1860-1889 cohort was four generations deep, and the detection of maternal and grandmaternal genetic effects require three and four generations, respectively. However, to investigate this possibility, we extended our analysis to subsequent cohorts and searched for genetic maternal and maternal-grandmother effects on P_{16}, survival to 16 years of age. We focussed on survival rather than fitness for two reasons. First, relevant human evolution models emphasize early (grand)child survival as a focus of (grand)maternal care (e.g., [4,15,17]). Second, we could enlarge our pool of phenotyped individuals because we were not restricted to use only those individuals with complete reproductive records. These cohorts were collections of individuals born between 1860-89, 1890-99, 1900-09, 1910-19, 1920-29, 1930-39, and 1940-49. The pedigree

grew in breadth and depth with each subsequent decadal cohort (presumably the power to detect maternal and grandmaternal genetic effects grew accordingly): the largest contained 18,339 maternal sibships and 5746 maternal-grandmother sibships (Supplemental Table 4). We found no evidence for either genetic maternal or maternal-grandmaternal effects on P_{16} (Supplementary Table 6). We conclude that this population was truly devoid of meaningful genetic (grand)maternal effects for survival.

Recent demographic changes might have eliminated or mitigated the influence of ancestral care. The study population migrated to the Utah Territory beginning in the 1840s, and whilst many of the individuals in the 1860-1889 cohorts can be associated with grandmothers in the pedigree, there is no guarantee that these ancestors co-migrated and provided care. Furthermore, fertility in this population was very high (married women born between 1870-1874, for example, produced an average of 7.0 live births each [23]), and infant mortality was relatively low compared to previous and contemporaneous populations [36]. These suggest that maternal and especially grandmaternal genetic effects might have been diluted by unusually large family sizes. However, this dilution should have been lessened over subsequent decadal cohorts because fertility was reduced [23] and the frequency of resident grandmothers likely increased as the colonization event receded into the past, but the genetic effects were still absent (see above).

DISCUSSION

The persistence of post-reproductive lifespan in women [4-6] appears even more puzzling, as we have exhaustively investigated all proposed evolutionary pathways and found no evidence for any source of response to selection for late-life female lifespan. We believe that the most likely explanation for this absence is that one or more genetic correlations involving late-life female survival were positive in the past. Genetic correlations are known to switch sign as

environments change [37], although the pattern of the direction of these changes are unclear [38]. Our results suggest that recent evolutionary processes are insufficient to explain the persistence of female lifespan. This interpretation highlights how little we understand how changes in human ecology may have altered the relationships between genes, lifespan, and fitness. More quantitative genetic analyses such as this should be applied to other human populations to understand better among-population distributions of relevant genetic correlations. The quantitative genetic approach introduced here provides a conceptual framework for future studies into human evolutionary demography, a field that has yet to embrace an indirect genetic perspective to understanding aging in a social context [39]. If genetic correlations are shown to vary among populations, new theory is needed to link these differences to changes in human ecology.

In contrast to the female results, we found strong evidence for genetic selection to favour late-life male lifespan, which may provide some explanation for the unusually long lifespan of humans compared to other primates and most other animals [40-42]. Counter to models of human lifespan that emphasize the evolutionary role of late-life male reproduction [2,13], direct selection was not the main cause of its genetic selection; instead indirect selection via early fitness in both males and females explained the majority of genetic selection. Future applications of this 'Animal Model' to this population may succeed in identifying at a finer scale which ages before 50 are the most important contributors. Our result has important consequences for evolutionary theories of ageing. The 'antagonistic pleiotropy' (AP) model [8] and its mechanistically-detailed application 'disposable soma theory' [43,44] argue that the attenuation of the strength of selection with increasing age will cause genes with advantageous early-life fitness effects but deleterious late-life mortality costs to spread through a population. This is expected to cause negative genetic correlations across early and late fitness traits [45], which we did not observe. 'Mutation accumulation' (MA) models [7] instead view ageing as a strictly maladaptive phenomenon where

264 acting deleterious mutations are allowed to accumulate due to relaxed selection. Whilst
265 traditional MA models assume that gene effects upon survival rates are completely age-
266 dependent [1,46], observations that mortality rates may not always increase with age in the very
267 old [47] have prompted the development of MA models that assume positive genetic correlations
268 between early function and late survival [12]. Our results support the existence of these positive
269 genetic correlations that suppress the evolution of senescence and promote longer life [48-50].

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Acknowledgements We thank the Pedigree and Population Resource of the Huntsman Cancer Institute, University of Utah (funded in part by the Huntsman Cancer Foundation) for its role in the ongoing collection, maintenance and support of the Utah Population Database (UPDB). We also thank Ken Smith for providing the data used in this study. CAW was funded by a NERC postdoctoral fellowship (NE/I020245/1) and a University of Edinburgh Chancellor's fellowship. We thank Arthur Gilmour, Jarrod Hadfield, Alastair Wilson for helpful technical advice. Comments from Josephine Pemberton, Loeske Kruuk, Daniel Nussey, Per Smiseth, Ben Whittaker, and five anonymous reviewers greatly improved this manuscript.

Author Contributions J.A.M. conceived the study. Both authors contributed to its design, analysis and interpretation, and both wrote the manuscript.

TABLES:

Table 1. Variance estimates from the best univariate 'Animal Models'. Estimates are given as the proportion of total phenotypic variance. Model selection details are given in Supplementary Table 1. Tests for significance compare the likelihoods of the simplest model that includes the effect to the next simplest model that does not. There was no test for significant residual effects variation, and all other variance components were significant to a threshold $p < 0.0001$. Dashes indicate variance components that were not estimated as part of the 'best' models (see Supplementary Table 7 for parameter estimates from rejected and more complex models).

Trait	Residual	Additive Genetic (narrow-sense heritability)	Maternal	Paternal Grandmother	Maternal Grandmother
w	0.842 (0.005)	0.118 (0.006)	0.020 (0.004)	0.017 (0.003)	0.012 (0.003)
♀LS_{50}	0.786 (0.010)	0.176 (0.009)	-	-	-
♂LS_{50}	0.761 (0.010)	0.232 (0.010)	-	-	-
♀w_1	0.803 (0.008)	0.161 (0.010)	0.026 (0.006)	-	-
♀P_{50}	0.917 (0.008)	0.078 (0.007)	-	-	-
♀w_2	0.997 (0.007)	-	-	-	-
♂w_1	0.827 (0.008)	0.129 (0.010)	0.034 (0.006)	-	-
♂P_{50}	0.921 (0.008)	0.038 (0.009)	0.036 (0.006)	-	-
♂w_2	0.945 (0.010)	0.043 (0.008)	-	-	-

Table 2. Estimated variance-covariance matrices from the best trivariate 'Animal Model' of fitness (*w*), post 50 female (♀LS_{50}) and post 50 male (♂LS_{50}) lifespan. Diagonals (grey shaded cells) contain variances, above the diagonal correlations, and below the diagonal covariances. The additive genetic covariances between *w* and sex-specific LS_{50} estimates genetic selection for increased post-50 lifespan for each sex. Pairwise likelihood ratio tests (Supplementary Table 3) determined whether genetic covariation differed significantly from zero: boldface estimates indicate $0.01 < p < 0.05$, * for $0.001 < p < 0.01$, ** for $0.0001 < p < 0.001$ and *** for $p < 0.0001$ (note that summaries of significance tests of genetic variances for all three traits and for intra-sex genetic LS_{50} correlations and are given in Supplementary Tables 1 and 4, respectively). The significance of residual covariances was not tested as these are not of direct interest here. The significance of (grand)maternal variances can be inferred from the results of the appropriate univariate models (Table 1). Parentheses indicate estimates of standard errors. Empty cells within the 'Residual' matrix indicate associations that are precluded by the trait definitions. Model selection details are given in Supplementary Table 3. Dashes indicate variance components that were not estimated as part of the 'best' models (see Supplementary Table 7 for parameter estimates from rejected and more complex models).

	w	♀LS_{50}	♂LS_{50}
Residual			
w	0.437 (0.003)	-0.019 (0.007)	0.003 (0.007)
♀LS_{50}	-0.132 (0.048)	105.09 (1.27)	
♂LS_{50}	0.016 (0.047)		93.04 (1.22)
Additive Genetic			
w	0.054 (0.003)***	-0.050 (0.034)	0.110 (0.031)**
♀LS_{50}	-0.057 (0.038)	23.83 (1.22)***	0.817 (0.032)***

$♂LS_{50}$	0.138 (0.039)**	21.48 (0.893)***	29.0 (1.24)***
Maternal			
w	0.010 (0.002)	-	-
Paternal Grandmother			
w	0.009 (0.001)	-	-
Maternal Grandmother			
w	0.006 (0.001)	-	-

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Table 3. Best estimates of the variance-covariance matrices for the seven components of fitness defined in this study. Values on the diagonals (grey shaded cells) are variances, those above the diagonal are correlations, and those below are covariances. Values in parentheses are estimates of standard errors. Empty cells indicate associations that are precluded by the trait definitions. Significance for residual or maternal effect covariation was not evaluated as these are not of direct interest in this study. Pairwise likelihood ratio tests (Supplementary Table 4) determined whether genetic covariation differed significantly from zero: boldface estimates indicate $0.01 < p < 0.05$, * for $0.001 < p < 0.01$, ** for $0.0001 < p < 0.001$ and *** for $p < 0.0001$. Summaries of significant tests of genetic variances for all seven traits are given in Supplementary Table 1. In addition, models were also fit with additive genetic correlations constrained to +/- 1 (whichever was closest to the estimate), and pairwise likelihood ratios tests determined significant departures from perfect correlations. All tests rejected perfect correlations with $p < 0.002$, except for the case of ♀P_{50} ♂P_{50} ($p = 0.71$).

Residual	♀LS_{50}	♂LS_{50}	♀w_1	♀P_{50}	♂w_1	♂P_{50}	♂w_2
♀LS_{50}	105 (1.27)		0.007 (0.007)				
♂LS_{50}		93 (1.22)			-0.002 (0.008)		0.021 (0.008)
♀w_1	0.048 (0.046)		0.440 (0.008)	0.533 (0.005)			
♀P_{50}			0.149 (0.002)	0.178 (0.002)			
♂w_1		-0.014 (-2.12)			0.388 (0.004)	0.553 (0.004)	0.684 (0.007)
♂P_{50}					0.145 (0.002)	0.176 (0.002)	

♂w_2		0.016 (0.006)			-2.7E-4 (-0.042)		0.006 (6.2E-5)
Additive Genetic	♀LS_{50}	♂LS_{50}	♀w_1	♀P_{50}	♂w_1	♂P_{50}	♂w_2
♀LS_{50}	24.3*** (1.22)	0.815*** (0.032)	-0.002 (0.034)	0.384*** (0.039)	-0.009 (0.039)	0.399*** (0.081)	0.071 (0.069)
♂LS_{50}	21.7*** (0.896)	29.0*** (1.24)	0.111* (0.033)	0.270*** (0.043)	**0.094** (0.036)	0.517*** (0.073)	0.220** (0.065)
♀w_1	-2.6E-3 (-0.426)	0.173* (0.051)	0.084*** (0.005)	0.549*** (0.033)	0.787*** (0.049)	0.456*** (0.096)	0.309*** (0.073)
♀P_{50}	0.237*** (0.024)	0.182*** (0.029)	0.020*** (0.002)	0.016*** (0.001)	0.483*** (0.052)	1.043*** (0.116)	0.101 (0.073)
♂w_1	-0.010 (0.045)	**0.120** (0.046)	0.054*** (0.003)	0.014*** (0.002)	0.057*** (0.005)	0.665*** (0.061)	0.273** (0.078)
♂P_{50}	0.165*** (0.028)	0.238*** (0.002)	0.012*** (0.002)	0.012*** (0.001)	0.014*** (0.002)	0.007*** (1.5E-4)	0.073 (0.105)
♂w_2	0.001 (0.001)	0.019** (0.006)	0.002*** (3.3E-4)	2.1E-4 (1.8E-4)	0.001** (2.9E-4)	1.0E-4 (1.5E-4)	2.7E-4*** (4.9E-5)

Maternal	♀w_1	♂w_1	♂P_{50}
♀w_1	0.013 (0.002)	0.650 (0.127)	0.464 (0.142)
♂w_1	0.010 (0.002)	0.038 (0.003)	0.613 (0.076)
♂P_{50}	0.005 (0.001)	0.007 (0.001)	0.007 (1.1-E4)

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Table 4. Multiple regression coefficients and phenotypic selection gradients for each fitness related trait analysed (symbols and traits are defined in the main text) There are no confidence intervals associated with these regression estimates because the multiple coefficient of determination was equal to one (leaving no residual variance).

	Estimate	**Proportion expressed**	**Phenotypic selection gradients**
(Intercept)	-0.854		
sex	-0.116	1	-0.116
♀w_1	1	0.500	0.500
♀P_{50}	0.000185	0.500	9.25E-5
♀w_2	1	0.367	0.367
♂w_1	1	0.500	0.500
♂P_{50}	0.0216	0.500	0.011
♂w_2	1	0.371	0.371

Table 5. Sources of post-50 lifespan response to selection. Each source (predicted response to selection) is the product of β_{wz}, the source trait's phenotypic selection gradient (Table 4) and the genetic covariance between sex-specific LS_{50} and the source trait (Table 3). Percentages of female LS_{50} response are not shown, as all female components were non-significant or negligible. Male standard errors follow from the product of the phenotypic selection gradients and the standard errors associated with genetic covariances. Bold-faced and boxed letters correspond to elements in the previously proposed evolutionary model pathways illustrated in Fig 1 or those pathways that we estimated to be important.

Trait	β_{wz}	**Genetic Covariance with *LS50***		**Predicted Response to Selection**		**% of ♂*LS50* Response**
		♀	♂	♀	♂	
♀w_1	0.5 **A**	-0.003 **D×L×E**	0.173 (0.051) **D×K×H**	-0.001	0.087 (0.025)	55.36
♀P_{50}	9.25E-5	0.237	0.182 (0.029)	<0.001	1.68E-5 (2.68E-6)	0.01
♂w_1	0.5 **C**	-0.010	0.120 (0.046) **J×Q×H**	-0.005	0.060 (0.023)	38.39
♂P_{50}	0.011	0.165	0.238 (0.002)	0.002	2.62E-3 (2.53E-5)	1.64
♂w_2	0.371 **B**	0.006 **I×N×E**	0.019 (0.006) **I×S×H**	0.002	0.007 (0.002)	4.60
Total change (in years/generation)				-0.002	0.156	

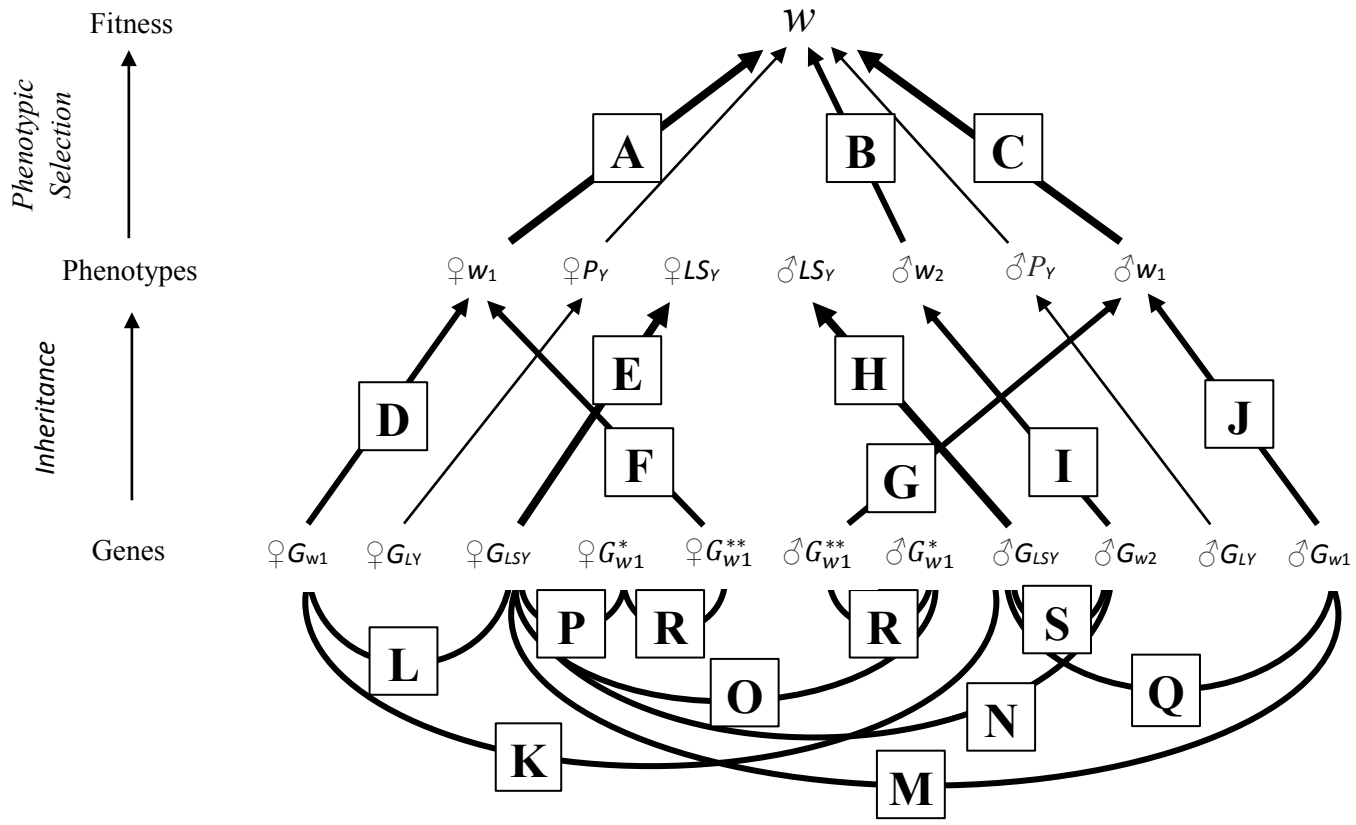

Figure 1. Causal diagram of hypothesized pathways by which selection for sex-specific lifespan beyond some female post-reproductive age *Y* could act. Traits are sex-specific fitness to age *Y* (w_1), survival to *Y* (P_Y), post-*Y* fitness (w_2), and post-*Y* lifespan (LS_Y). $G_{subscript}$ indicates genes for these traits. $♀_{w1}^{*}$ and $♂_{w1}^{*}$ are genes for an effect of an individual on its (grand)offspring's early fitness (i.e. indirect genetic effects), and $♀_{w1}^{**}$ and $♂_{w1}^{**}$ are those genes expressed in a social partner (in this case the mother or grandmother as we only consider (grand)maternal effects). See main text for more details.

METHODS: ***Study population*****:**

We used individual records of humans collected by the Utah Population Database, a descendant-based genealogical database. These records included information on years of birth and death and the identities of mothers and fathers for individuals born up to 1950 and the descendants of these (1,732,394 unique individuals). In our primary analyses, we constrained our focal population to those individuals with mothers who reproduced between 1860 and 1889 to limit effects of secular trends and to restrict our sample size to allow computationally tractable analyses. We also included all siblings of these individuals who were born outside of this time window. Only those individuals that were indicated by the Database to have known years of death and complete reproductive histories were analysed. Individuals with insufficient information to describe all fixed effects (see *Fixed effects* below) were excluded from the study. This left 128,129 informative individuals in the phenotyped generation. Phenotypes were assigned only to these individuals, but the pedigree used in the analyses was generated from the union of the focal population and all individuals born prior to 1890. This pedigree contained 179,759 individuals with a depth of up to four generations (enough to detect any grandmaternal genetic effect variance). Fitness (see below) followed from birth records contained in the complete database.

This was a pre-contraception population with large family sizes [23]. For individuals born in the years 1860-1889, the expected number of offspring ranged between four and six, depending upon the year of birth [51]. Survival rates were generally low (Supplementary Figure 1). For these reasons, Malthusian growth rates were positive for all birth year cohorts, ranging from 0.007 to 0.024 (Supplementary Figure 2). The predominant residency pattern at this time was neolocal, with first degree relatives living in close proximity to newly married individuals [52]. In a study of one Utah county in 1880, Mineau and Anderton [53] estimated that within the first five years of marriage involving a man 22.5 years or younger, 71% of couples lived in the same

community or county as at least one of his parents. 13% of these couples lived in the same house as his parent.

Study traits: As selection is defined in terms of the covariance between relative fitness and traits of interest, we calculated the relative fitness *w* of individuals using the individual reproductive value at birth. This is an index trait defined as one-half the number of children born (*LRS*), with each annual contribution discounted by the Malthusian growth rate characteristic for each birth-year cohort [54]. Thus, for any individual *i* born at year *k*, its relative fitness is $w_{ik} = \frac{1}{2}\sum_{j=1}^{\infty} M_{ijk}e^{-r_k j}$, where M_{ijk} is the number of offspring born to individual *i* at age *j* and r_k is its cohort's Malthusian growth rate. Individual *LRS* divided by the cohort-specific mean was also calculated, but these were not considered further as they correlated extremely well with *w* (r = +0.986). Relative fitness was also calculated over two age ranges (up to 50 years of age and 50+) by summing annual fitness contributions over the appropriate age intervals to arrive at w_1 and w_2. The threshold age of 50 was chosen because it represented an age beyond which female reproduction was negligible and therefore unlikely to be under meaningful direct selection. Other threshold ages could be reasonably used for other applications of the Animal Model to understanding the genetics of lifespan. The heritability analysis (see below) revealed no evidence for heritable variation for post-50 female fitness. Survival to 50 years, P_{50}, was defined as a binary trait (1 = success, 0 = failure). Years lived beyond 50 (LS_{50}) and the aforementioned fitness traits were sex-specific: trait values of 'NA' were assigned to all individuals of the alternative sex. We defined the traits w_2 and LS_{50} to be conditioned upon successful survival to 50. Those individuals that failed to survive to 50 were assigned values of 'NA' for these traits.

Phenotypic selection gradient estimation: Sex and sex-specific P_{50}, w_1, and w_2 collectively explained all variation for relative fitness (R^2 = 1) in a multiple regression when 'NA' values were treated as non-existent data [55]. This approach has been used previously to re-derive

Hamilton's indicators from a multiple regression perspective [24,54] and to estimate phenotypic selection gradients for other traits in this population [56]. Estimates for phenotypic selection gradients are given in Table 4. Although there was selection for sex (a partial covariance between relative fitness and sex holding other traits constant), this trait was not analysed further as it could not contribute to an indirect response to selection for any trait because it has no genetic variance. Viewed from a quantitative genetic perspective, there is no variation for direct genetic effects on sex because the sex of offspring cannot be predicted by the sex of the parents (every individual invariably has only one parent of each sex). Whilst maternal genetic effects of sex ratio can exits, in theory, the absence of maternal genetic effect variance for relative fitness in this case (see Results), indicate that any such IGEs present in this population do not contribute to trait evolution.

This approach to estimating phenotypic selection gradients imputes nominal trait values for individuals for which trait values are not logically permitted to be expressed (e.g., male-limited traits in females or late-acting traits in individuals that died early) [55]. The imputed values are equal to the mean trait values of the fraction of the population that is allowed to express the trait. Indicator, or 'dummy', variables signal whether or not imputed values are used for particular individuals. Multiple indicator variables can be used simultaneously and individual indicators can themselves be imputed if their expression is also logically precluded from some portion of the population. Consider the post-50 contribution to male relative fitness, $♂w_2$, for example. As only males that survive to be 50 are exposed to direct phenotypic selection for this trait, three variables must be considered: 'sex', $♂P_{50}$ (male survival to 50), and $♂w_2$. The trait 'sex' acts as an indicator for $♂P_{50}$: males are either '0' or '1' and all females are given a nominal value of 0.743, as this is the fraction of male births that survive to age 50. The trait $♂P_{50}$ acts as an indicator for $♂w_2$: male survivors are awarded trait values according to the amount and timing of post-50 reproduction, and all females and males that die before 50 are

assigned the nominal value 0.0216, because that is the mean value amongst the male survivors for $♂w_2$.

All traits and indicator variables are included in the multiple regression. Multivariate selection gradients follow from the estimated partial regression coefficients, with each gradient weighted by the proportion of the population that has the trait. For our example above, the partial regression coefficient for $♂w_2$ is one (because late-age derived relative fitness is, by definition, still relative fitness), but the phenotypic selection gradient for $♂w_2$ is 0.371 because only 74.3% of born males survived to 50, and only half of all births are male. Phenotypic selection gradients for 'conditioned' traits (those traits that are expressed only individuals that have particular values for other traits) provide correct predictions for the multivariate response to selection when applied to a multivariate breeder's equation [21], but care should be taken to understand the conditional nature of these traits when interpreting these phenotypic selection gradients on their own. For example, variation in early male fitness $♂w_1$ and late male fitness $♂w_2$ does not collectively explain all of the fitness variation in males because there is a mean total relative fitness difference between males that do and do not survive to 50. That difference is not derived from post-50 differences (because the imputation strategy equates the expected values $♂w_2$ of the two groups). Fitness variance derived from selection for $♂P_{50}$ is also needed to completely describe total male fitness variance, and this selection follows from the difference between survivors and non-survivors for mean $♂w_1$ values. In this example, phenotypic selection for $♂P_{50}$ is small but positive (+0.011) because individuals that survive to 50 generate slightly more fitness before 50 than those that do not survive. A negative phenotypic selection gradient for this trait would not have been illogical. Indeed, it might be expected when early fitness is associated with large costs to mid-life survival.

***Genetic and environmental variance/covariance estimation*:** Human studies of lifespan heritability have traditionally used either twin-based [29,30,57] or family clustering [58-60]

approaches. The former can account for otherwise misleading effects of shared environments, but appropriate datasets are rare. Conversely, the latter are applicable to a wider range of datasets, but there may be problems with common environments. Neither use all available information efficiently when large pedigrees contain individuals of many different degrees of relatedness. 'Animal Models', a form of linear mixed-effect models, offer an alternative approach to decomposing phenotypic variances and covariances into additive genetic and environmental components [18,61]. This approach uses pedigrees to construct matrices containing pairwise relatedness between all individuals; this allows the most efficient possible use of all available phenotypes.

The mixed-effect approach allows simultaneous estimation of fixed effects that may contribute to phenotypic variance but may confound estimates of genetic (co)variation if they are not identified. The random effects generally include additive genetic and environmental effects (residuals), but when the models are specified to include effects associated with shared mothers, they can partition the residual variance further into maternal effect variance and a new residual effect variance. It should be emphasized that while these maternal effects can include the influence that the mothers' have upon the phenotype of their offspring beyond the genes that they transmit, they will also include other aspects of the environment that is shared by individuals with the same mothers (e.g., socioeconomic status shared amongst siblings). Important to this study is that the mixed model can be specified so as to partition the maternal effect variance into two more components: 1) the maternal indirect genetic effect (IGE) variance (the part of the maternally-produced environmental variance that is heritable) and 2) the maternal indirect environmental effect (IEE) variance (the part of the maternally-produced variance that is not-heritable). Following this same logic, models can be further specified to include grandmaternal effect, and these can be likewise partitioned into grandmaternal IGEs and grandmaternal IEEs. For these models, the grand-maternal IEE variance will include the

effects of environment common to all individuals that share the same grandmother. The residual variance is generated by environmental variance due to effects that are not shared by siblings (in all models) or by cousins (the models that include grandmaternal effect terms).

Associations between genetic relatedness and common environmental effects have the potential to bias estimates of additive genetic variance if the source of common environment is not specified in the mixed models. For example, individuals that live in the common areas but happen to share a great-grandparent might resemble each other more than would be expected from sharing 1/32 of their genes. If the effects of area are not included in the model, then estimates of genetic variance will be inflated unless grandparental effects are fit. The pedigree depth of four generations used here is sufficient to discriminate between genetic and non-genetic causes of phenotypic similarity amongst first cousins, but common environments shared between more distantly-related individuals could, in principle, bias our results. However, our models find very small and statistically insignificant grandparental and maternal genetic effects. Failing to include these in the models has no material effect on our estimates of additive genetic variance. Given that common environmental effects between first cousins are unimportant, it seems unlikely that common environment shared between more distantly related individuals would bias our results in meaningful ways.

Grandpaternal effects were not modelled in this study for two reasons. First, grandmaternal and grandpaternal effects are likely to be conflated by tractable mixed models, and the grandmaternal effect variance that we estimated already accounts for these sources of phenotypic variation. Second, what we identify as ‘grandmaternal’ effects are both very small and lacking evidence for a heritable basis, and therefore decomposing this variance was unlikely to reveal any interesting genetic covariation. Any environmental effects common to individuals with a shared grandfather will contribute to the grandmother IEE variance or the maternal IIE variance (for models with and without fit grandmaternal effects, respectively).

Fixed effects: Our set of candidate fixed effects were: year of birth, age of mother at birth, and three parameters that described the birth order amongst siblings with a shared mother (number of older siblings, number of individuals born in the same year, and number of younger siblings). For sex-specific LS_{50} and all fitness traits, we used ASReml 4.0 [62] to fit univariate fixed effect models using the set of candidate fixed effects as factors. This software implements restricted maximum-likelihood (REML) to jointly estimate fixed and random effects. Whilst not all fixed effects had a significant effect on all traits (as determined by Wald-tests), every fixed effect had a significant effect on at least one trait (Supplementary Table 2). As random effect variances estimated from mixed models are conditioned upon the fixed effects, we used the entire set of candidate fixed effects in all subsequent models to simplify the interpretation of genetic architecture.

Univariate 'Animal Models': For all analysed traits, variance components and random effect structures were first investigated using univariate 'Animal Models' of the general form

$$\mathbf{y} = \mu + \mathbf{Xb} + \mathbf{Zu} + \mathbf{e} \quad (1)$$

Where **y** is a vector of phenotypes, μ is the mean, **b** is a vector of the fixed effects described in the previous section, **u** is a vector of random effects, **X** and **Z** are design matrices linking individual records to the appropriate fixed and random effects, and **e** is a vector of residual errors. For each trait, models were fit with one random effect corresponding to additive genetic effects, and the Akaike Information Criterion (AIC) were measured from this fit. If this AIC was lower than that derived from the model with residuals defined as the only random effect, then a new model was fit that added maternal effects as an additional random effect. If this yielded an even lower AIC score, then the maternal effect term was replaced with a maternal genetic and a maternal residual term and a new model was fit. For each trait, we used AIC to define the best model (Supplementary Table 1), and the random effects included within these

were incorporated into the subsequent multivariate analyses. Because, as expected, the best model of ♀w_2 had no additive genetic effect variance; this trait was not included in further analyses. For w, the model with maternal genetic effect variance fit slightly better than the model with unspecified maternal effects. In this case, an additional model was considered in which paternal grandmother and maternal-grandmother effects replaced maternal genetic effects. This dual-grandmother effect model provided the best AIC values, but follow-up models that sought to partition these into genetic and non-genetic grandmother effects failed to produce meaningful results. AIC and likelihood ratio tests were used to select best models and to test for significant variance terms in all univariate analyses.

Multivariate 'Animal Models' – total genetic selection for LS_{50}: We estimated genetic covariances between sex-specific LS_{50} and w using trivariate equivalents of the 'Animal Models' represented in equation (1), where **y** represented a matrix of phenotypes for each of the traits measured, and μ was a vector of means for each phenotypic trait. Each model included fixed, additive genetic, and residual effects for all traits. Maternal effects for fitness were also included. Three models were compared: 1) unconstrained genetic covariances; 2) the genetic covariance between fitness and female lifespan was constrained to be zero; and 3) the genetic covariance between fitness and male lifespan was constrained to be zero (Supplementary Table 3). The comparison of models 1 and 2 tests for a genetic covariance between fitness and female lifespan of greater than zero, and the comparison of models 1 and 3 allows the test for the same parameter for males.

Multivariate 'Animal Models' – components of genetic selection for LS_{50}: Genetic covariances between sex-specific LS_{50} and w were explored at a finer scale by replacing w with heritable fitness determinants in a multivariate 'Animal Model'. As the univariate analyses found significant maternal effect contributions only for ♂w_1 , ♀w_1, and ♂P_{50}, maternal effects were fitted only for these traits in the multivariate analyses. The full multivariate model failed to

converge when $\male P_{50}$ was included, but it did successfully converge when this trait was removed. Thus, to estimate genetic covariances between $\male P_{50}$ and LS_{50} in both sexes and all sex-specific heritable fitness components, we used six independent bivariate analyses. Results from all seven models are joined in Table 3.

As the larger multivariate model took many weeks to converge, we judged that complete hypothesis testing involving all constrained versions of this model was impractical. Pairwise bivariate models were used instead. For each trait pair, three 'Animal Models' were fit: 1) a model with unconstrained genetic covariances; 2) a model with genetic covariance constrained to be zero; 3) a model with genetic correlations constrained to be +/- 0.9999 (depending upon the direction of the genetic correlation estimated by the unconstrained model). The AIC values for all of these models were compared (Supplementary Table 4).

Decadal cohort analyses: These were performed as described in the *Univariate 'Animal Models'* methods section, except survival to 16 years of age (P_{16}) was the only trait considered, and univariate models were applied independently to individuals born in each of the decades between 1890 and 1949 (plus siblings). As before, individuals with insufficient data to define fixed effects or exact age at death were excluded from the analyses, but complete reproductive histories were not required for inclusion in the decadal cohort analyses of survival to 16. Relevant sample sizes for all cohorts are given in Supplementary Table 5. Also, once the model progression indicated the presence of additive genetic for P_{16} (as it did for all cohorts), two new models were fit. The first replaced the maternal term with maternal genetic and environment terms. The second additional model kept the maternal term and added a maternal-grandmother term. If the latter model was preferred (this happened only once), then a final model was fit that replaced the maternal-grandmother term with maternal-grandmother genetic and environment terms. AIC and likelihood ratio tests were used to select best models for each cohort (Supplementary Table 6).

***Method for predicting a univariate response to selection*:** Two methods are widely used for predicting evolutionary change due to natural selection over one generation. The univariate 'breeder's equation' [63,64] uses the product of a selection gradient and additive genetic variance associated with a trait of interest. The 'Robertson-Price Identity' [65,66] uses instead the genetic covariance between relative fitness and the trait of interest. Under ideal circumstances, when the trait of interest does not correlate with another trait with a causal relationship with fitness, the two approaches yield the same result. However, under more realistic conditions, such as when one wishes to predict a response to selection in a wild or otherwise uncontrolled population, the 'breeder's equation' can yield misleading results [67], and the 'Robertson-Price Identity' is recommended [68]. There appears to be no advantage to using the 'breeder's equation' when the means exist to estimate the genetic covariance between relative fitness and the trait of interest. The present study adopts the 'Robertson-Price' approach to estimate a response to selection for post-lifespan (Part 1: Estimating net genetic selection for late-life lifespan) because correlations between lifespan and traits with causal effects on fitness is central to evolutionary models of post-reproductive lifespan (see Fig. 1). No such issues exist with our application of the 'multivariate breeder's equation' in Part 3 because all possible fitness traits are considered simultaneously in our estimate of selection gradients (the multiple coefficient of determination for the regression of fitness on all fitness traits is one).

Data and code availability statement: The data that support the findings of this study are available from the Pedigree and Population Resource of the Huntsman Cancer Institute, University of Utah, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of the Huntsman Cancer Institute.

Human research participants: We have complied with all relevant ethical regulations. Ethical review of this study was provided by an IRB administered through the Office of the Vice President for Research at the University of Utah. Informed consent was impossible as all subjects are deceased.

Supplementary Table 1. Model comparisons for univariate Animal Models. All mixed models include the same set of fixes effects (Supplementary Table 2) and residual random effects. Other effects correspond to additive genetic (G), maternal (M), maternal genetic (G_M), maternal residual (E_M), paternal grandmother (PGM), and maternal grandmother (MGM). Boldface values identify the 'Best' model selected by AIC. Models with estimated variances that are bound at zero are excluded. Note that ♀w_2 was analysed, but the 'G' model yielded an estimate of genetic variance that was bound at zero. Details regarding the estimated size of random effects left out of the 'Best' model are given in Supplementary Table 7.

Trait	**Random effects**	**LogL**	***k***	**AIC**	*D*	*P*
w	-	-63478.8	1	126959.7	-	-
	G	-62293.4	2	124590.8	2370.9	<0.0001
	G + M	-62237.9	3	124481.7	111.02	<0.0001
	G + G_M + E_M	-62236.27	4	124480.5	3.2	0.0736
	G + M + PGM + MGM	**-62179.72**	**5**	**124369.4**	**116.3**	**<0.0001**
♀LS_{50}	-	-23982	1	46067.92	-	-
	G	**-23564.5**	**2**	**45535.2**	**543.7**	**<0.0001**
	G + M	-23563.6	3	45536.84	0.36	0.5485
♂LS_{50}	-	-23982	1	47965.98	-	-
	G	**-23564.5**	**2**	**47132.92**	**835.06**	**<0.0001**
	G + M	-23563.6	3	47133.1	1.82	0.1773
♀w_1	**-**	-32090.2	1	64182.3	-	-
	G	-31594.7	2	63193.4	990.9	<0.0001
	G + M	**-31584**	**3**	**63174.04**	**21.36**	**<0.0001**
♀P_{50}	-	-32250.2	1	64502.46	-	-
	G	**-32167**	**2**	**64338.06**	**166.4**	**<0.0001**
	G + M	-32166.2	3	64338.44	1.62	0.2031

♂w_1	-	-32130.5	1	64262.9	-	-
	G	-31717.7	2	63439.38	825.52	<0.0001
	G + M	**-31698.5**	**3**	**63403.08**	**38.3**	**<0.0001**
	G + G_M + E_M	-31698.2	4	63404.4	0.68	0.4096
♂P_{50}	-	-32230.8	1	64463.62	-	-
	G	-32149.4	2	64302.76	162.86	<0.0001
	G + M	**-32131.6**	**3**	**64269.14**	**35.62**	**<0.0001**
♂w_2	-	-23839.2	1	47680.36	-	-
	G	**-23821.9**	**2**	**47647.82**	**34.54**	**<0.0001**
	G + M	-23821.1	3	47648.2	1.62	0.2031

Supplementary Table 2. Fixed effect estimates from the best univariate Animal Models (conditional F-statistics).

Trait	Variance	Source of Variation	Numerator *df*	Denominator *df*	*F*-statistic	*P*
w	0.515	mean	1	6994.4	60043.47	<.001
		sex	2	125751.9	440.43	<.001
		birth year	88	123740.4	3.37	<.001
		maternal age	46	125278.9	1.25	<.001
		# same-age siblings	2	120995.4	126.6	<.001
		# older siblings	16	119997.8	4.95	<.001
		# younger siblings	16	119874.8	2.34	0.002
♀LS_{50}	133.901	mean	1	6761.7	1.5E+6	<.001
		birth year	86	45242.0	18.09	<.001
		maternal age	41	46184.1	1.34	0.069
		# same-age siblings	2	46846.2	0.23	0.790
		# older siblings	15	45046.7	1.22	0.244
		# younger siblings	15	44899.9	1.38	0.147
♂LS_{50}	123.258	mean	1	7623.4	1.3E+6	<.001
		birth year	85	44900.2	4.97	<.001
		maternal age	44	46677.8	1.14	0.246
		# same-age siblings	2	45902.9	0.94	0.390
		# older siblings	15	44816.7	0.72	0.771
		# younger siblings	15	44370.5	1.48	0.105
♀w_1	0.544	mean	1	6650.0	77605.55	<.001
		birth year	86	61357.4	2.26	<.001
		maternal age	41	62554.9	1.69	0.004

		# same-age siblings	2	57944.6	53.07	<.001
		# older siblings	15	60249.2	5.39	<.001
		# younger siblings	15	60102.1	2.65	<.001
♀P_{50}	0.195	mean	1	5422.6	1.3E+5	<.001
		birth year	86	63080.7	1.81	<.001
		maternal age	41	63576.8	2.05	<.001
		# same-age siblings	2	59960.7	90.52	<.001
		# older siblings	15	62632.2	2.04	0.010
		# younger siblings	15	62527.5	0.97	0.481
♂w_1	0.467	mean	1	6308.0	74232.61	<.001
		birth year	86	61793.0	1.00	0.491
		maternal age	45	63050.6	1.22	0.152
		# same-age siblings	2	55987.0	79.89	<.001
		# older siblings	15	60087.6	6.43	<.001
		# younger siblings	16	9909.9	3.90	<.001
♂P_{50}	0.191	mean	1	3720.8	1.5E+5	<.001
		birth year	86	63072.6	2.04	<.001
		maternal age	45	63494.0	1.00	0.464
		# same-age siblings	2	53487.6	95.59	<.001
		# older siblings	15	61433.5	1.13	0.324
		# younger siblings	16	61402.9	1.17	0.286
♂w_2	0.0064	mean	1	4279.7	3073.11	<.001
		birth year	85	47168.0	7.43	<.001
		maternal age	44	47333.4	0.60	0.985
		# same-age siblings	2	47223.6	0.59	0.554
		# older siblings	15	46900.9	1.44	0.117
		# younger siblings	15	46819.0	0.62	0.860

Model selection details are given in Supplementary Table 1.

Supplementary Table 3. Model comparisons for total genetic selection Animal Models. All models include the entire suite of fixed effects. Maternal effects variance was fit for fitness only.

Model	**LogL**	D	$P\{r_G = 0\}$
Unconstrained	-108623.60	-	-
$\text{cov}_G(w, ♀LS_{50}) = 0$	-108624.70	2.2	0.138
$\text{cov}_G(w, ♂LS_{50}) = 0$	-108629.94	12.68	0.0004

Supplementary Table 4. Model comparisons for pairwise trait covariances. All models include the entire suite of fixed effects. Maternal effects variances/covariances are fit when the appropriate best univariate models indicate their presence.

Trait pairs		Model	LogL	D	$P\{r_G = 0\}$	$P\{r_G = \pm 1\}$
♀LS_{50}	♂LS_{50}	unconstrained	-46033.77	-	-	-
		$r_G = +1$	-46049.77	32.00	-	<0.0001
		$r_G = 0$	-46330.06	560.58	<0.0001	-
	♀w_1	unconstrained	-54339.60	-	-	-
		$r_G = -1$	-54500.27	321.34	-	<0.0001
		$r_G = 0$	-54340.78	2.36	0.1245	-
	♀P_{50}	unconstrained	-54903.81	-	-	-
		$r_G = +1$	-54950.64	93.66	-	<0.0001
		$r_G = 0$	-54932.63	57.64	<0.0001	-
	♂w_1	unconstrained	-54463.48	-	-	-
		$r_G = -1$	-54500.27	73.58	-	<0.0001
		$r_G = 0$	-54464.14	1.32	0.2506	-
	♂P_{50}	unconstrained	-54881.11	-	-	-
		$r_G = +1$	-54886.97	11.72	-	0.0006
		$r_G = 0$	-54897.17	32.12	<0.0001	-
	♂w_2	unconstrained	-46587.28	-	-	-
		$r_G = +1$	-46604.44	34.32	-	<0.0001
		$r_G = 0$	-46587.50	0.44	0.5071	-
♂LS_{50}	♀w_1	unconstrained	-55144.06	-	-	-
		$r_G = +1$	-55300.97	313.82	-	<0.0001
		$r_G = 0$	-55148.47	8.82	0.0030	-
	♀P_{50}	unconstrained	-55713.92	-	-	-

		$r_G = +1$	-55778.26	128.68	-	<0.0001
		$r_G = 0$	-55731.49	35.14	<0.0001	-
	♂w_1	unconstrained	-55259.13	-	-	-
		$r_G = +1$	-55374.89	229.52	-	<0.0001
		$r_G = 0$	-55261.60	4.94	0.0262	-
	♂P_{50}	unconstrained	-55667.51	-	-	-
		$r_G = +1$	-55672.29	9.56	-	0.0020
		$r_G = 0$	-55696.03	57.01	<0.0001	-
	♂w_2	unconstrained	-47347.62	-	-	-
		$r_G = +1$	-47363.36	31.48	-	<0.0001
		$r_G = 0$	-47353.33	11.42	0.0007	-
♀w_1	♀P_{50}	unconstrained	-53418.44	-	-	-
		$r_G = +1$	-53495.51	154.14	-	<0.0001
		$r_G = 0$	-53481.45	126.02	<0.0001	-
	♂w_1	unconstrained	-62953.50	-	-	-
		$r_G = +1$	-62962.84	18.68	-	<0.0001
		$r_G = 0$	-63055.64	204.28	<0.0001	-
	♂P_{50}	unconstrained	-63659.25	-	-	-
		$r_G = +1$	-63664.51	10.52	-	0.0012
		$r_G = 0$	-63671.95	25.40	<0.0001	-
	♂w_2	unconstrained	-55394.83	-	-	-
		$r_G = +1$	-55407.40	25.14	-	<0.0001
		$r_G = 0$	-55405.92	22.18	<0.0001	-
♀P_{50}	♂w_1	unconstrained	-63820.15	-	-	-
		$r_G = +1$	-63861.07	81.84	-	<0.0001
		$r_G = 0$	-63865.57	88.84	<0.0001	-
		unconstrained	-64213.44	-	-	-

	♂P_{50}	r_G = +1	-64213.51	0.14	-	0.7083
		r_G = 0	-64298.60	170.32	<0.0001	-
	♂w_2	unconstrained	-55988.37	-	-	-
		r_G = +1	-56005.18	33.62	-	<0.0001
		r_G = 0	-55988.94	1.14	0.2857	-
♂w_1	♂P_{50}	unconstrained	-52004.73	-	-	-
		r_G = +1	-52010.76	12.06	-	0.0005
		r_G = 0	-52023.75	38.04	<0.0001	-
	♂w_2	unconstrained	-55510.94	-	-	-
		r_G = +1	-55524.42	26.96	-	<0.0001
		r_G = 0	-55518.19	14.50	0.0001	-
♂P_{50}	♂w_2	unconstrained	-55953.35	-	-	-
		r_G = +1	-55961.87	17.04	-	<0.0001
		r_G = 0	-55953.48	0.26	0.6101	-

Supplementary Table 5. Cohort size and number of maternal and maternal grandmother sibships. '*N*' is the number of individuals with valid values for all fixed effects (probands). These are exclusive of the individuals that were excluded from the analyses due to incomplete information (counts of these are given under "Incomplete Individuals"). 'Pedigree' refers to the number of informative unique individuals in the pedigree.

Cohort	***N***	**Pedigree**	**Unique Maternal Sibships**	**Unique Maternal grandmother sibships**	**Sires**	**Sires of Sires**	**Dams of Sires**	**Dams**	**Sires of Dams**	**Dams of Dams**
1860-89	122.926	245,549	5763	722	37994	9099	9937	41898	11179	12270
1890-99	133,074	253,543	7916	1554	47085	12392	13716	50188	15725	17324
1900-09	155,552	305,596	11,681	3003	63887	17417	19030	67257	22953	25128

1910-19	163,670	356,871	16,550	4798	86229	23462	24861	89531	32204	34898
1920-29	131,873	338,854	18,339	5746	95710	26237	27085	98615	38816	41390
1930-39	71,635	249,834	14,571	4893	84998	22907	23176	86881	38942	40746
1940-49	39,826	210,386	11,756	3886	81729	20570	20623	82696	39107	40171

Supplementary Table 6. Animal Model comparisons for multiple cohort analyses (P_{16}). All mixed models include the same set of fixes effects (Supplementary Table 2) and residual random effects. Other random effects correspond to additive genetic (G), maternal (M), maternal genetic (G_M), maternal residual (E_M), maternal grandmother (MGM), maternal grandmother genetic (G_MGM), and maternal grandmother residual (E_MGM). Boldface values identify the best model selected by AIC and likelihood ratio tests. Models with estimated variances that are bound at zero are excluded. Pairwise comparisons for ΔAIC and *LRT* tests involve nested models only.

Cohort	Model	LogL	*k*	AIC	ΔAIC	*P*(LRT)
1860-89	-	-61529.7	1	123061.5		
	G	-61367.4	2	122738.8	-322.64	<0.0001
	G + M	**-61334.6**	**3**	**122675.2**	**-63.6**	**<0.0001**
1890-99	-	-66562.3	1	133126.6		
	G	-66369.2	2	132742.5	-384.12	<0.0001
	G + M	**-66357.1**	**3**	**132720.2**	**-22.28**	**<0.0001**
1900-09	-	-77658.4	1	155318.9		
	G	-77433.4	2	154870.8	-448.1	<0.0001
	G + M	**-77414.1**	**3**	**154834.3**	**-36.5**	**<0.0001**
1910-19	-	-81424.4	1	162850.7		
	G	-81149.2	2	162302.3	-548.36	<0.0001
	G + M	**-81119.8**	**3**	**162245.7**	-56.68	**<0.0001**
	G + M + MGM	-81119.3	4	162246.5	0.84	0.2815
1920-29	-	-65398.5	1	130799		
	G	-65213.9	2	130431.7	-367.26	<0.0001
	G + M	-65173.5	3	130353	-78.7	<0.0001
	G + G_M + E_M	-65172.6	4	130353.3	0.26	0.1871
	G + M + MGM	**-65170.7**	**4**	**130349.5**	**-3.528**	**0.0187**

1930-39	-	-35157.4	1	70316.78		
	G	-35027.7	2	70059.44	-257.34	<0.0001
	G + M	**-35004.1**	**3**	**70014.18**	**-45.26**	**<0.0001**
	G + G_M + E_M	-35004	4	70015.96	1.78	0.6390
	G + M + MGM	-35003.5	4	70014.94	0.76	0.2655
1940-49	-	-19388.3	1	38778.68		
	G	-19302.1	2	38608.28	-170.4	<0.0001
	G + M	**-19285.7**	**3**	**38577.3**	**-30.98**	**<0.0001**

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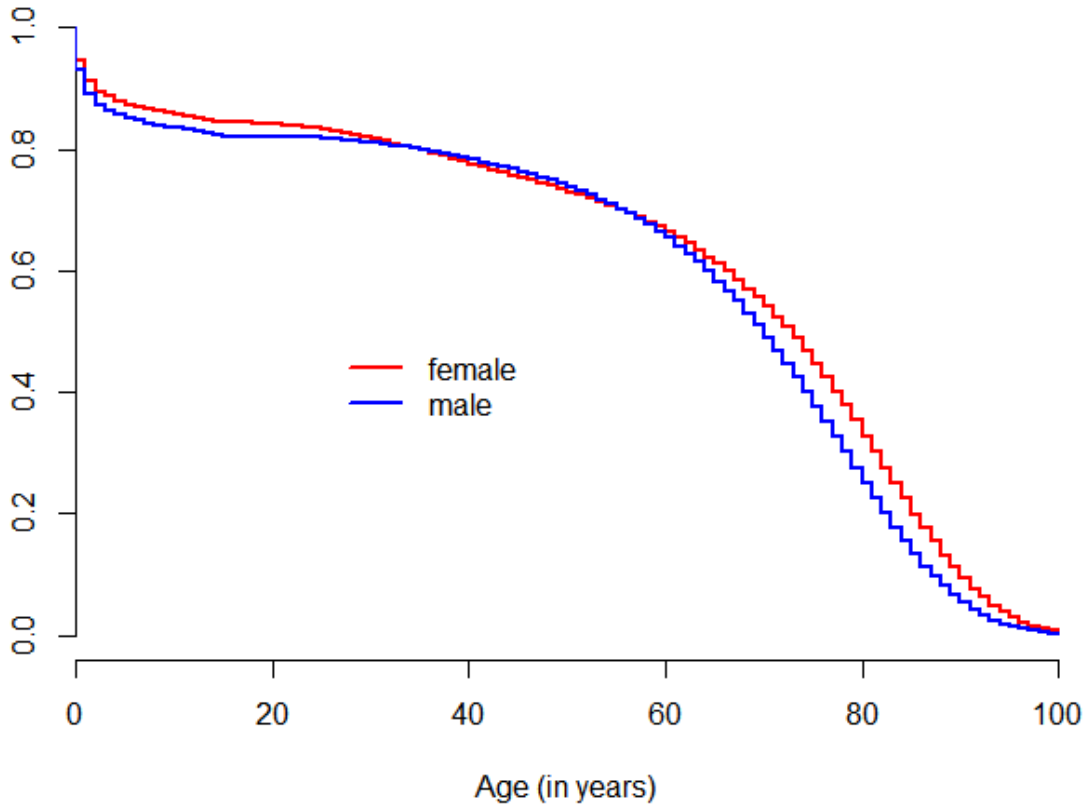
Supplementary Table 7. Estimates of variance estimates from simplest rejected models. 'Best' models were preferred over the simplest rejected models; the latter were associated with random effect variances judged to be insignificant. All mixed models include the same set of fixes effects (Supplementary Table 2) and residual random effects. Other random effects correspond to additive genetic (G), maternal (M), maternal genetic (G_M), maternal residual (E_M), paternal grandmother (PGM), and maternal grandmother (MGM).

Trait	Random effects from the 'Best' model	Rejected random effect of interest	Estimate from rejected model
w	A + M + PGM + MGM	G_M*	0.008 (0.005)
♀LS_{50}	A	M	0.004 (0.007)
♂LS_{50}	A	M	0.010 (0.007)
♀w_1	A + M	G_M	Bounded at zero
♀P_{50}	A	M	0.007 (0.006)
♀w_2	-	A	Bounded at zero
♂w_1	A + M	G_M	0.006 (0.008)
♂P_{50}	A + M	G_M	Bounded at zero
♂w_2	A	M	0.009 (0.007)

*Models with any combination of G_M, PGM, and MGM could have been reasonably chosen as the next model. However, models with PGM and MGM yielded estimates bounded at zero that caused these models to be rejected as candidates for 'Best' Model. The model with G_M did not produce bounded variance estimates.

Supplementary Figure 1. Cumulative sex-specific survival rates for the study population.



Supplementary Figure 2. Population growth rate change over time